Review Article

Nanotechnology in Action: Targeted Therapies for Leishmaniasis

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ABSTRACT

Leishmaniasis, a neglected tropical disease caused by Leishmaniadonovani, continues to threaten the health of over 350 million people in more than 90 countries, leading to approximately 50,000 deaths each year. Current treatments, including liposomal Amphotericin B, pentavalent antimonial, and miltefosine, face significant limitations such as reduced efficacy, toxicity, adverse side effects, drug resistance, and high costs. These challenges highlight the urgent need for alternative treatment strategies that can improve patient outcomes. Nanotechnology presents a promising avenue by providing advanced drug delivery systems that enhance bioavailability, minimize toxicity, and offer targeted therapeutic approaches. This review delves into the recent progress in nanodrug delivery systems (nDDSs) for treating leishmaniasis, with a focus on developments from the last five years. While preclinical studies have shown promising results, more extensive research is needed to move these innovations into clinical practice. Essential areas for advancement include molecular diagnostic techniques, comprehensive clinical trials, and standardization efforts to facilitate the transition of these novel solutions into widely accessible treatments.

Keywords: Nanomedicine, Leishmaniasis, Nanolipid Carriers, Polymeric Nanoparticles, Metallic Nanoparticles.

1. INTRODUCTION

Leishmaniasis, a neglected tropical disease caused by Leishmaniadonovani, poses a significant health risk to over 350 million people across more than 90 countries, resulting in an estimated 50,000 deaths annually.[1,15] Existing treatments, such as liposomal Amphotericin B, pentavalent antimonial, and miltefosine, are hindered by limited efficacy, toxicity, side effects, drug resistance, and high costs. These limitations underscore the pressing need for alternative treatment methods that can improve patient outcomes.[2,16,25,39]

Nanotechnology offers a promising path by enabling advanced drug delivery systems that increase bioavailability, reduce toxicity, and provide targeted therapeutic delivery[13,47,60]. This review examines recent advancements in nano drug delivery systems (nDDSs) for the treatment of leishmaniasis, with an emphasis on developments from the past five years.[15,16]Although preclinical results have been promising, further research is required to advance these innovations to clinical application[25]. Key areas for future progress include the development of molecular diagnostic tools, comprehensive clinical trials, and standardization practices to accelerate the adoption of these new treatment strategies.[3,4,5,6]

2. LITERATURE SURVEY:

2.1 Problem Statement:

Leishmaniasis is a severe and often overlooked parasitic disease that presents a significant health burden in many parts of the world.[16] Transmitted by the bite of an infected female phlebotomine sand fly, the disease manifests primarily in tropical and subtropical regions. It results in an estimated 0.7 to 1.0 million new cases each year and causes approximately 20,000 to 30,000 deaths annually.[8,16] the region's most heavily impacted include countries like Bangladesh, Brazil, India, Ethiopia, Sudan, and South Sudan.

This study focuses on understanding the disease's complexity, the current treatment landscape, and potential innovative solutions.[9,16,21]

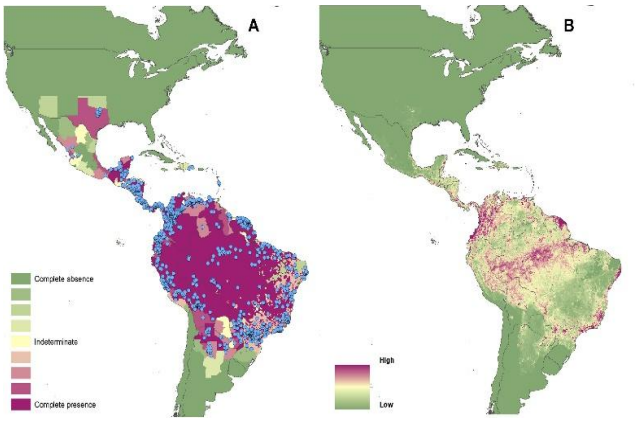

Figure 1: Reported and predicted distribution of cutaneous leishmaniasis in the New World.

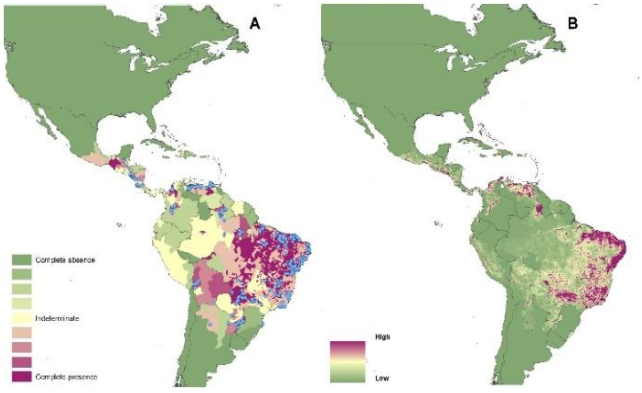

Figure 2: Reported and predicted distribution of visceral leishmaniasis in the New World.

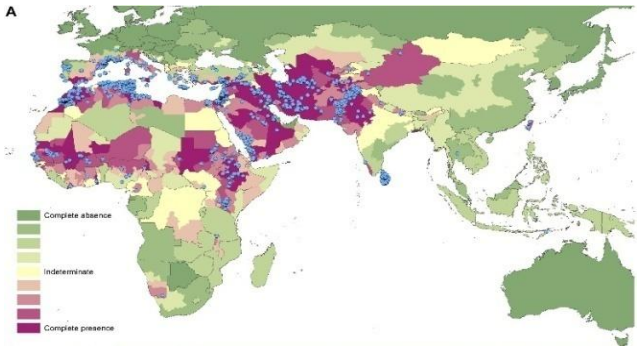

Figure 3: Reported and predicted distribution of cutaneous leishmaniasis in the Old World.

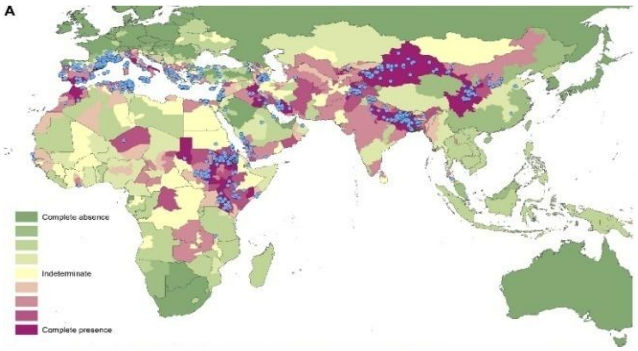

Figure 4: Reported and predicted distribution of visceral leishmaniasis in the Old World.

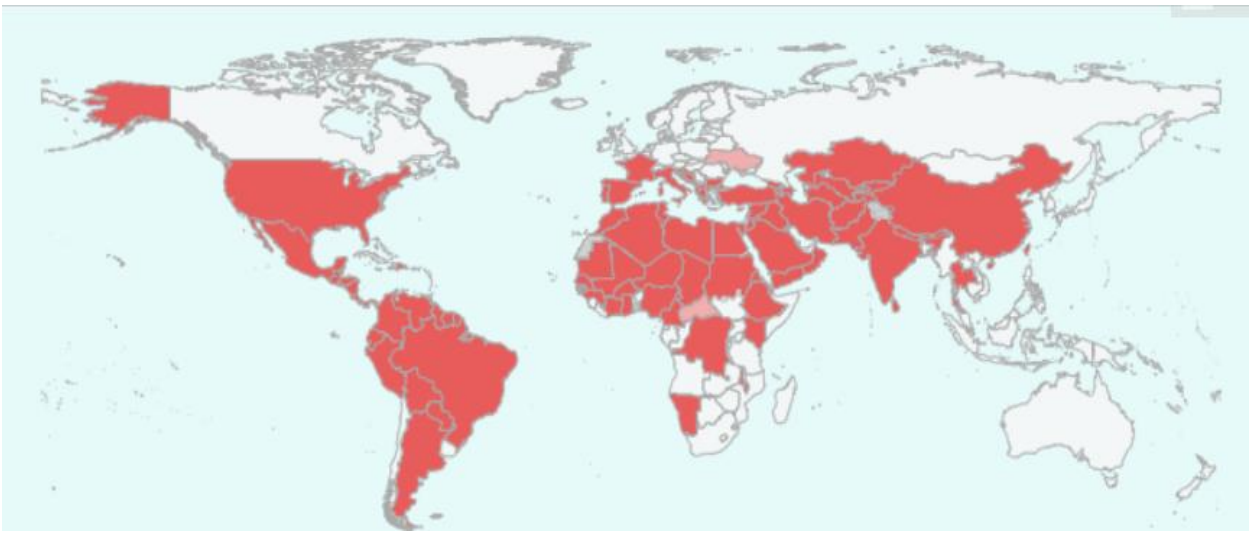

Figure 5: Status of endemicity of Cutaneous Leishmaniasis: 2023

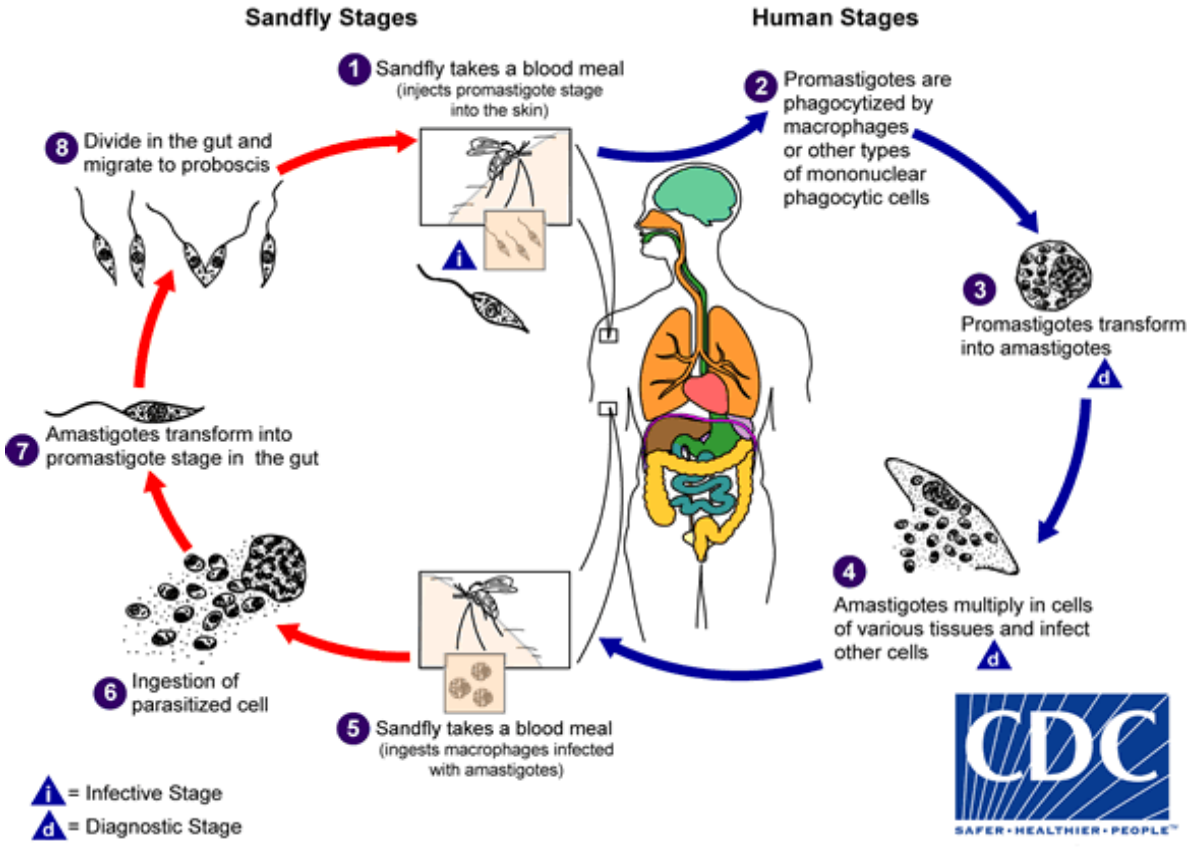

Figure 6: Life Cycle of Leishmania

2.1.1 Objective:

The primary objective of this study is to explore and evaluate the limitations of current leishmaniasis treatment methods, with a focus on the parasite's lifecycle and host interactions. Additionally, the study aims to investigate the potential of nano drug delivery systems (nDDSs) as a breakthrough approach to improving the efficacy, targeting, and safety of treatments.[10,25,31,32]

2.1.2 Life Cycle of Leishmania:

Leishmaniasis transmission occurs when a female phlebotomine sand fly (fig. 5), active primarily from dusk until dawn, bites a mammalian host. The life cycle of the Leishmania parasite consists of two primary stages: the promastigote (P.G.) phase and the amastigote (A.G.) phase.[17]

In the P.G. phase, the parasite is flagellated, allowing it to move freely through the sandfly's gut. After feeding on blood from a mammalian host, the sandfly injects the promastigote form into the host's skin during its bite.[14]The injected parasite is then engulfed by the host's mononuclear cells through phagocytosis, where it transforms into the amastigote form, also known as the Leishman-Donovan body.[10]

Inside the host's reticuloendothelial system, the amastigotes reproduce and mature, which can result in either an asymptomatic or symptomatic form of the disease, depending on the host and the specific species of Leishmania involved. Amastigotes can disseminate via the bloodstream and lymphatic system, resulting in either visceral or mucosal forms of the disease.

Recent studies have also revealed a potential co-infection between Leishmania species such as L. Vianniabraziliensis and L. V. guyanensis, with RNA viruses like LRV, which trigger an excessive immune response via toll-like receptors. This response can lead to metastasis and mucosal damage, though the precise link between the presence of the virus and clinical severity remains inconclusive.

2.1.3. Current Leishmaniasis Treatment and Their Limitations:

Leishmaniasis treatment relies on a limited number of antileishmanial drugs, and both first- and second-line therapies are constrained by several challenges[25]. Although the World Health Organization (WHO) has approved meglumine antimonate (M.A.) for all forms of leishmaniasis, it still recommends the development of newer treatments due to various limitations associated with the existing drugs.[39]

For patients who develop resistance to first-line drugs for visceral leishmaniasis (V.L.), amphotericin B (Amp B) is considered a viable alternative. Amp B targets ergosterol, a key component of the parasite's cell membrane, increasing membrane permeability and triggering ion efflux, which leads to the disruption of the cell and parasite death. However, resistance to Amp B can occur when changes in the ergosterol precursor prevent effective binding, making the drug less effective. Other options include highly toxic drugs such as paromomycin and pentamidine, as well as oral medications like miltefosine and sitamaquine. These drugs are sometimes used together to enhance treatment effectiveness and reduce side effects.[19,39]

Despite their potential, these medications often require long treatment courses, which can result in poor patient adherence and contribute to resistance. Additionally, the inability of these drugs to penetrate the phagolysosomes of macrophages, where the amastigote forms of the parasite replicate, limits their effectiveness. The varying drug sensitivities of different Leishmania species also make treatment complicated. Furthermore, resistance mechanisms, such as redox signaling, help the parasites survive the oxidative stress imposed by activated macrophages during phagocytosis. Patients with weakened immune systems, such as those infected with HIV, are at higher risk of treatment failure and relapse[28,48,50,53]

These issues underscore the urgent need for novel treatment approaches that minimize side effects and prevent resistance. Addressing the development of drug resistance in leishmaniasis requires a comprehensive strategy, including the combination of drugs with different mechanisms of action to limit resistance[17]. Tailoring treatments based on Leishmania species and geographical factors could also improve efficacy. Research into new agents and optimized drug delivery systems, like liposomal formulations, is critical for overcoming resistance by ensuring targeted drug release [22,23,29]. Furthermore, understanding resistance at the genetic and molecular level will help design more effective treatments. Strong surveillance systems, early detection of resistance, and adaptable treatment plans are crucial to managing resistance. Investigating host-pathogen interactions may also offer valuable insights for enhancing the host's immune response as a therapeutic strategy. Collaboration between researchers, pharmaceutical companies, and healthcare professionals is essential to accelerate the development of new therapies and effectively combat leishmaniasis resistance.[17]

2.1.4. Nanodrug delivery systems utilized during leishmaniasis treatment:

Conventional chemotherapy for leishmaniasis has numerous limitations, including high costs, the need for injections, severe toxicity, and the growing concern of drug resistance. These challenges necessitate the exploration of alternative therapies for effective management. Advances in translational sciences, fueled by innovations in interdisciplinary research, have played a significant role in improving the treatment landscape for infectious diseases.[60] One such innovation is nanomedicine, which utilizes nanodrug delivery systems (nDDSs) to enhance the delivery of therapeutic agents and diagnostic tools. This field has seen rapid growth and holds great promise for improving the treatment of leishmaniasis.[25,39]

Transforming conventional antileishmanial drugs into nanodrug delivery systems has demonstrated notable improvements in pharmacokinetic properties.[51]This approach has garnered significant attention in the research community, as it holds the potential to enhance drug effectiveness while reducing toxicity. By encapsulating drugs in nanocarriers, these systems provide more precise and targeted drug delivery, ensuring the drug reaches its intended site of action more efficiently, while minimizing side effects.[58] Additionally, nDDSs enable controlled and sustained drug release within the body's circulatory system, significantly improving therapeutic outcomes.[39,60]

The size, charge, hydrophobicity, and encapsulated molecule of nanodrug delivery systems profoundly influence their absorption, distribution, and overall effectiveness[53]. The size and charge of these nanoparticles (NPs) affect how they interact with cells, including their ability to penetrate cell membranes and interact with immune cells. Hydrophobicity plays a role in the interaction of nanoparticles with proteins and immune cells, influencing uptake and distribution. These factors all contribute to the particle's behavior in the body, dictating their success in treating infections like leishmaniasis.[40,41]

Phagocytosis is a key process in which immune cells such as macrophages, neutrophils, and monocytes engulf particles larger than 0.75 nm, facilitating the uptake of drug-loaded nanocarriers into these cells.[22,24,46] Since the Leishmania parasite primarily infects macrophages but also targets other phagocytic cells like neutrophils and adipocytes, this phagocytic activity presents an ideal opportunity for targeted drug delivery. By utilizing nanocarriers that can be ingested through phagocytosis, drugs can be delivered directly to infected cells, ensuring higher intracellular concentrations while reducing systemic toxicity. This method allows for the use of lower drug doses with enhanced efficacy.[18,54,55]

Nanoparticles can also be "vectored" using active or passive techniques. Active vectoring involves modifying the surface of the nanoparticles with specific chemicals, whereas passive vectoring utilizes the body's natural ability to identify and remove foreign particles. An example of promising active vectoring involves ferritin, a protein with a cage-like structure, which can encapsulate drugs and transport them to macrophages, where the Leishmania parasite resides. This strategy enhances drug delivery to infected cells, improving therapeutic outcomes and minimizing side effects associated with conventional systemic drug administration. Additionally, ferritin-based silver nanoparticles (NPs) have shown potential for depositing silver within macrophages, providing a means to treat leishmaniasis more effectively.[51,55]

However, the transition of nanomedicines from the laboratory to clinical practice faces several significant obstacles. High production costs, the complexity of formulation, and long development timelines are some of the key barriers that hinder the widespread use of nDDSs in leishmaniasis treatment. These challenges are particularly evident in the case of visceral leishmaniasis (V.L.).[19,42] The lack of reproducibility and the intricacy of nanomedicine formulations remain critical issues, slowing down their adoption beyond academic research. To overcome these challenges, researchers are focusing on integrating robust characterization methods and implementing quality-centric protocols throughout the development process. Strategies such as quality by design, process analytical technology, and microfluidic approaches are being explored to streamline production, scale-up, and evaluation, ultimately facilitating the clinical application of nanomedicines for treating leishmaniasis.[54]

Below are some Nanodrug delivery systems utilized during leishmaniasis treatment -

a) Nanolipid Carriers (NLCs):

Nanolipid carriers (NLCs) are an advanced generation of lipid nanoparticles designed to overcome limitations of SLNs. NLCs offer higher drug loading capacity and stability, making them promising carriers for difficult-to-deliver drugs. Studies on ursolic acid and diselenide-loaded NLCs for VL treatment have shown improved therapeutic outcomes, including better immune responses and lower parasitic burden. These NLCs also offer a higher margin of safety compared to traditional treatments, suggesting their potential for more effective and safer VL therapies.[24,46,29]

In conclusion, lipid-based nanoparticles, including liposomes, SLNs, and NLCs, show significant promise for VL treatment by improving drug delivery, enhancing efficacy, and minimizing side effects. However, further research is needed to optimize their clinical applications.[40]

b) Polymeric Nanoparticles (PNPs):

PNPs have gained significant attention due to their small size, biocompatibility, and controlled drug release. They are made from both biodegradable and non-biodegradable polymers.[23,30]

Non-biodegradable polymers (e.g., PMMA, polyacrylamide) were initially used but raised concerns due to chronic toxicity.

Biodegradable polymers (e.g., chitosan, alginate, PLGA, PLA) are preferred for their lower toxicity and better biocompatibility.[23,30,34,43,49,57,59]

Applications in Leishmaniasis:

PLGA-based nanoparticles loaded with mannosylatedthiolatedparomomycin (MTP) showed enhanced macrophage uptake and significant antileishmanial effects in vivo, reducing parasite load in infected mice by 3.6 times.[38]

c) Metal and Metal Oxide Nanoparticles:

Metallic Nanoparticles:

Silver, gold, titanium oxide, and zinc oxide, have been studied for their potential in Leishmania treatment.

Silver NPs (SNPs): Demonstrated significant antileishmanial activity by inducing apoptosis in Leishmania major promastigotes and reducing lesions in mice.[58]

Gold NPs (GNPs): Showed therapeutic efficacy against Leishmaniatropica and L. donovani, with enhanced activity when functionalized with Amp B. Gold nanoparticles also have applications in detecting Leishmania through various assays.[41,51]

Copper NPs: Exhibited synergistic toxicity against L. major in combination with meglumineantimoniate, improving cutaneous lesions in infected mice.

Metal Oxide Nanoparticles:

Iron oxide NPs: Coated with peptides and loaded with Amp B showed effective treatment by reducing parasite burden.[58]

Zinc oxide NPs: Synthesized using plant extracts (e.g., Verbena officinalis), showed significant antileishmanial activity and were found to be more effective when smaller in size.

Silver-doped zinc oxide NPs: Demonstrated effectiveness by generating ROS, degrading parasite DNA, and exhibiting antileishmanial properties.[41]

d) Silica Nanoparticles:

Mesoporous silica NPs (MSNs) are ideal for drug delivery due to their large surface area and ability to release drugs in a controlled manner.

Copper-doped silica NPs loaded with artemisinin (ART) showed significant antileishmanial effects, maintaining drug efficacy and preventing resistance.

Dye-loaded silica NPs can be used as biosensors to detect Leishmania in biological samples.[52,60]

e) Carbon Nanotubes:

Carbon nanotubes (CNTs) are emerging as promising tools for drug delivery in leishmaniasis treatment. They can be functionalized to enhance biocompatibility and provide therapeutic effects without causing toxicity.

CNTs functionalized with cisplatin exhibited potent antileishmanial activity in vitro, with better performance than conventional drugs like Glucantime.[55]

f) Nanocomposites:

Metallopolymernanocomposites, which combine the properties of metals and polymers, have been widely explored for biomedical applications.

A silver NP-polyvinylpyrrolidone nanocomposite exhibited significant antileishmanial activity against *Leishmania amazonensis*, inducing ROS stress and ultrastructural changes in the parasites.[40,46]

2.1.5 Treatment Approach:

Researchers have developed multiepitope vaccines utilizing PLGA nanoparticles (NPs) in combination with the adjuvant monophosphoryl lipid A (MPLA) or modified with an octapeptide targeting tumor necrosis factor receptor II. These nanoparticles are coated with chimeric peptides that include HLA-restricted epitopes from three key immunogenic proteins of *Leishmania infantum*: kinetoplastid membrane protein, cysteine peptidase A, and histone H1. This configuration induces a robust T-cell immune response, primarily driven by CD8+ T cells and CD4+ TH1 cells. Additionally, the nanovaccine promotes dendritic cell maturation, contributing to protective immunity against visceral leishmaniasis (VL). Importantly, PLGA NPs serve as a biocompatible delivery system for the vaccine.[33,36,59]

In a related study, a nanovaccine was designed using PLGA NPs for delivering the multiepitope peptide of Leishmania's cysteine protease A (CPA 160−189), coencapsulated with MPLA. Subcutaneous administration of this nanovaccine to BALB/c mice led to a strong T-cell response specific to CPA 160−189. This immune response was characterized by elevated levels of TNFα, IL-2, IgG1/IgG2a, and IFN-γ production, while levels of IL-10 and IL-4 remained low. After four months, a substantial reduction in parasite load was observed in the liver and spleen, indicating sustained protective immunity.[28,44,58]

Another study focused on a nanovaccine utilizing PLGA NPs loaded with lipophosphoglycan (LPG) and autoclaved Leishmania antigen (ALA) or soluble Leishmania antigen (SLA). This vaccine demonstrated increased nitric oxide production in macrophages and elevated expression of IL-12 and IFN-γ cytokines. It provided 80% protection against VL, accompanied by a significant T-cell response, particularly marked by the high expression of Th1 cytokines.[28]

Further studies on nanovaccines for leishmaniasis include the development of a lipid nanoparticle-based vaccine loaded with plasmid pVAX1-NH36, which is under investigation. Additionally, a therapeutic strategy was developed involving paromomycin (PM)-loaded mannosylatedthiomeric nanoparticles specifically designed for the treatment of visceral leishmaniasis. The enhanced macrophage uptake and reduced parasite load in both in vitro and in vivo models showed therapeutic efficacy several times greater than PM alone .[40] Lastly,DNA nanovaccines incorporating dendrimer and poly(methyl methacrylate) (PMMA) nanoadjuvants have demonstrated effectiveness by inducing immune responses and reducing the parasite load in Leishmania major-infected BALB/c mice.[28,44,53]

3. METHODS:

3.1 Implementation Methodology:

Leishmaniasis transmission begins when a female phlebotomine sand fly, which is nocturnally active, bites a mammalian host. The life cycle of the Leishmania parasite comprises two primary stages: the promastigote (P.G.) phase and the amastigote (A.G.) phase. During the P.G. phase, the parasite is flagellated, enabling free movement within the sandfly's gut. When the sandfly feeds on a mammalian host, it injects the promastigotes into the host's skin through its bite. This initial transmission sets off a complex interaction with the host's immune response, which triggers phagocytosis. The promastigote is then engulfed by the host's mononuclear cells, particularly macrophages, where it transforms into the non-flagellated amastigote form. [40,41]

Once inside the host's mononuclear cells, the parasite thrives by manipulating host cell functions and evading immune defenses. This intracellular environment within macrophages in the spleen, liver, and bone marrow is critical for the parasite's survival and proliferation. Such an existence complicates treatment as drugs must penetrate these cells effectively. The amastigotes replicate and persist in these cells, contributing to the spread of the disease within the host.[60]

Furthermore, recent research indicates that some Leishmania species, such as *L. Vianniabraziliensis* and *L. V. guyanensis*, can harbor RNA viruses like Leishmania RNA virus (LRV). This co-infection can provoke an excessive immune response through toll-like receptor pathways, which can lead to tissue damage and metastasis. The precise mechanisms by which LRV exacerbates the severity of leishmaniasis remain a topic of ongoing investigation, but evidence suggests that the presence of LRV correlates with increased clinical complications, such as mucosal involvement and relapse.[54]

3.2 Current Treatments:

Conventional treatment options for visceral leishmaniasis involve the use of antimonial drugs, amphotericin B, and miltefosine. However, these treatments come with significant challenges, including toxicity, high costs, and long administration periods. Antimonial compounds, for instance, are known to cause severe side effects such as pancreatitis, cardiotoxicity, and liver dysfunction, making treatment adherence difficult for patients.

Amphotericin B is effective but requires intravenous administration under hospital supervision. This can lead to nephrotoxicity, placing an additional burden on healthcare systems and patients in resource-limited settings. [57]

Miltefosine, the first oral drug approved for leishmaniasis treatment, showed promise due to its easier administration and broad-spectrum efficacy. Nevertheless, its usage is marred by reports of gastrointestinal disturbances, teratogenic effects, and the emergence of drug resistance, particularly in endemic regions like the Indian subcontinent. Drug resistance has become a significant concern, driven by suboptimal dosing, incomplete treatment courses, and genetic variations in Leishmania species.

Efforts to counteract these limitations include combination therapies, which leverage the synergistic effects of multiple drugs to improve treatment outcomes.[39,60]

3.3 Advancements in Nanodrug Delivery Systems (nDDS):

To address these challenges, research has shifted towards exploring innovative solutions, such as nanodrug delivery systems (nDDS). These systems utilize nanotechnology to enhance drug delivery by improving bioavailability, targeting, and controlled release. By encapsulating antileishmanial drugs within nanoparticles, it is possible to achieve better penetration into macrophages where the *Leishmania amastigotes* reside. This targeted approach increases drug efficacy while minimizing systemic toxicity.[42,45]

Nanoparticles, including liposomes, polymeric nanoparticles, and dendrimers, have been studied for their potential to revolutionize leishmaniasis treatment. Liposomal amphotericin B, for instance, has already proven effective by significantly reducing nephrotoxicity compared to conventional formulations. Polymeric nanoparticles offer additional benefits, such as biodegradability and the ability to conjugate with ligands for active targeting, further enhancing the selectivity of drug delivery.[60,56]

Research has shown that nanoparticles can be engineered to bypass the reticuloendothelial system and deliver their payload directly to infected macrophages, increasing drug concentration at the site of infection. This approach not only reduces the required dosage but also enhances treatment outcomes and patient adherence. Additionally, controlled release mechanisms within nDDS help maintain therapeutic drug levels over extended periods, reducing the frequency of administration and improving patient convenience.[29,48,50]

While the application of nanotechnology in treating leishmaniasis is promising, it is still in the experimental stage for widespread use. Clinical trials and regulatory evaluations are necessary to confirm the safety, cost-effectiveness, and scalability of these advanced delivery systems. However, preliminary results underscore the potential of nDDS to transform the current treatment landscape, making it a pivotal focus of future research.[55]

4. DISCUSSIONS:

4.1 Analysis of Current Treatments:

Despite decades of research, the treatment of leishmaniasis remains inadequate, presenting a range of challenges including toxicity, treatment failures, and drug resistance. The complexity of the disease, with its ability to persist within the macrophages of vital organs, adds to the difficulty of finding comprehensive solutions. Current pharmacological interventions are often associated with severe side effects and require long durations of

administration, which can be prohibitive for affected populations.[29,59]

4.1.1 Advances in Nanodrug Delivery Systems (nDDSs):

Recent research has shifted towards nanotechnology-based drug delivery systems, which have demonstrated potential in improving the effectiveness of leishmaniasis treatments. Nanodrug delivery systems can enhance drug bioavailability, enable targeted delivery to infected macrophages, and reduce systemic toxicity. These systems leverage the unique properties of nanoparticles, such as their size, surface modification capabilities, and ability to carry both hydrophilic and hydrophobic drugs.[47,60]

Studies have shown that using nanocarriers such as liposomes, dendrimers, and polymeric nanoparticles can significantly increase drug stability and efficacy. Liposomal formulations of amphotericin B, for example, have shown reduced nephrotoxicity and better patient outcomes. Moreover, nDDSs can be engineered to respond to specific physiological conditions, such as pH variations within macrophages, ensuring the drug is released precisely where it is most needed.[31,45]

4.1.2 Case Studies and Comparative Analysis:

Case studies from high-incidence countries like India and Brazil highlight the effectiveness of implementing nDDSs in clinical trials. Comparative studies between conventional treatments and nDDSs have demonstrated reduced treatment durations, fewer side effects, and improved patient compliance.[15,16]

5. CONCLUSIONS:

A comprehensive examination of the Leishmania parasite's lifecycle, coupled with a critical analysis of current treatment options and recent advancements in nanotechnology-based drug delivery systems, has underscored the need for innovative treatment solutions. While traditional treatments have been somewhat effective, they fall short in terms of safety, efficacy, and accessibility. The integration of nanotechnology offers a promising pathway for the development of targeted and more effective treatments that could address these limitations and contribute to global health improvements.[47,60]

5.1 Future Scope and Further Enhancement of the Project

Future research should prioritize optimizing nanodrug delivery mechanisms to increase their precision and adaptability. Additionally, exploring novel compounds that can be integrated into nanocarriers, as well as the development of vaccines to offer long-term immunity, will be critical for comprehensive disease management. Collaborative research involving interdisciplinary teams will further enhance our understanding and contribute to more robust solutions.[17,58,55]

5.1.1 Deliverable

The primary deliverable for this project will be an exhaustive report that encompasses the background of leishmaniasis, a thorough analysis of treatment challenges, an exploration of nanotechnology-based solutions, and recommendations for future research directions. This report will serve as a valuable resource for researchers and policymakers working toward eradicating leishmaniasis and improving treatment protocols worldwide.[11,12,16]

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